REMARKS

I. Status of the Claims

Claims 1-31 have been cancelled and claims 32-58 have been added in this amendment. Support for new claims 32-58 can be found in the application as originally filed. For the Examiner's convenience, Applicants point out in the following table exemplary written description support in the original specification for the elements of the new claims.

Claim(s)	Elements	Exemplary Support
32-41, 47-58	A pharmaceutical composition comprising a marine oil	Page 14, lines 32-34
32-41, 47-58	A marine oil comprising eicosapentaenoic ethyl ester and docoshexaenoic acid ethyl ester	Page 15, lines 6-9
32-58	Eicosapentaenoic ethyl ester and docosahexaenoic acid ethyl ester in a pharmaceutically effective concentration to therapeutically treat hypertriglyceridaemia	Page 2, lines 5-9; page 14, lines 26-31; page 15, lines 6-11; original claim 23
32-, 34-37, 43, 47, 48, 53, 54, 57, 58	A concentration of brominated flame retardants in the pharmaceutical composition is less than 0.2 ug/kg as measured by the concentration of BDE 47	Example 6
33, 39, 44, 49, 55	A concentration of brominated flame retardants in the pharmaceutical composition is less than 0.1 μg/kg as measured by the concentration of BDE 47	Example 6
34	the sum of PCDDs and PCDFs in the marine oil is less than 4.65 pg/g	Example 5 and Fig. 2
35, 38, 39, 40, 41, 45, 46, 50, 56	the sum of TE-PCB in the marine oil is less than 22.6 pg/g	

Claim(s)	Elements	Exemplary Support
36, 40, 51, 57	An acid value about 0.2 mg KOH/g	Examples 8 and 9
37, 41, 52, 58	An acid value between 0.2 mg KOH/g and 0.3 mg KOH/g	Examples 8 and 9
42-46	A pharmaceutical composition prepared from a marine oil	Page 14, lines 26-27
42-44	A pharmaceutical composition prepared by reducing the concentration of brominated flame retardants as measured by the concentration of BDE 47 in the marine oil	Page 14, lines 20-26, Example 7
45, 46	A pharmaceutical composition prepared from a marine oil	Page 14, lines 20-26,
45, 46	A pharmaceutical composition prepared by reducing the sum of TE-PCB as measured in the marine oil	Example 5 and Fig. 2
42-46	increasing the concentration of eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester in the marine oil to a pharmaceutically effective concentration to therapeutically treat hypertriglyceridaemia	Page 2, lines 5-9; page 14, lines 26-31; page 15, lines 6-11; original claim 23
47-58	A method of treating at least one cardiovascular disease comprising administering a pharmaceutical composition comprising a marine oil	Page 15, lines 1-3
48-52, 54-58	The at least one cardiovascular disease is hypertriglyceridaemia	Page 15, lines 10-11

Accordingly, the present specification provides written description support for new claims 32-58. The parent application, PCT/IB03/02827, filed June 8, 2003, also fully supports the new claims, as does SE 0202188-9, filed July 11, 2002. The parent

PCT application and the present application both claim the benefit of priority of the July 11, 2002, filing date. Accordingly, the "critical date" of the present application is no later than July 11, 2002.

II. Information Disclosure Statement

Applicants have submitted herewith an Information Disclosure Statement. It is Applicants' understanding that none of those documents teach or suggest all of the presently claimed elements and/or do not enable the claimed compositions or methods, at least because, prior to the present invention, reduction and/or removal of brominated flame retardants, TE-PCBs and/or dioxin-like PCBs was not possible.

Certain of the documents submitted herewith discuss a commercial product called Omacor®. That product is supplied as a liquid-filled gel capsule for oral administration. Each one-gram capsule contains at least 900 mg of the ethyl esters of omega-3 fatty acids, approximately 840 mg of which are eicosapentaenoic acid (EDA) ethyl ester (approximately 465 mg) and docosahexaenoic acid (DHA) ethyl ester (approximately 375 mg). Omacor® is approved by the U.S. Food & Drug Administration (FDA) for use to reduce very high (≥ 500 mg/dL) triglyceride levels in adult patients, as an adjunct to diet. Accordingly, Applicants believe that new claims 32-58 read on Omacor® and that FDA-approved indication.

Omacor® was approved in the U.S. in November 2004, and was launched shortly thereafter. It was first registered in Norway in 1994. Omacor® was not sold in the U.S. before July 11, 2002, the priority date of the present application, and the sale of Omacor® is therefore not prior art to the instant claims.

As discussed in other documents submitted herewith, clinical trials using Omacor® were conducted in the U.S. prior to the July 11, 2002, priority date. However, those clinical trials did not constitute public uses. It is Applicants' understanding that confidentiality restrictions were imposed, control over Omacor® samples was exercised, and there was no commercial exploitation of Omacor® samples during those clinical trials.[1] Accordingly, the clinical trials performed in the U.S. prior to the July 11, 2002, priority date did not constitute a public use.

Applicants also submit herewith issued U.S. patents that read on Omacor®. For example, Applicants submit herewith U.S. Patent Nos. 5,502,077, 5,656,667, and 5,698,594, which are listed in the FDA's Orange Book for Omacor®. Applicants also submit herewith other published information concerning Omacor®. Applicants do not believe that any of those documents anticipate or render obvious the present claims at least because they do not teach or suggest all of the presently claimed elements and/or do not enable the claimed compositions and/or methods.

Applicants sold certain products under the brandname "EPAX" in Europe. Documents pertaining to those products are submitted herewith. *See, e.g.,* EPAX marketing information, information from http://www.epax.com, and product specifications for EPAX 1050TG, EPAX 4020EE, EPAX 4020TG, EPAX 4510TG, EPAX

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[1] The Federal Circuit revisited the area of public use in *SmithKline Beecham Corp. v. Apotex, Inc.*, 365 F.3d 1306 (Fed. Cir. 2004), holding invalid the patent-in-suit as anticipated by pre-critical date clinical trials. A year later, that opinion was withdrawn by an *en banc* court of the Federal Circuit. *SmithKline Beecham Corp. v. Apotex, Inc.*, 403 F.3d 1328 (Fed. Cir. 2005). In any event, *SmithKline Beecham* is distinguishable from the instant situation because there were no "apparent confidentiality restrictions on the patients or the administering physicians" involved in the clinical trials, and indeed the patentee did not even "question the public disclosure of its clinical trials." *SmithKline*, 365 F.3d at 1317.

5500EE, EPAX 6000EE, EPAX 6000TG, EPAX 6015EE, and EPAX 6015TG. "TG" in the EPAX product names indicates that the product contains omega-3 fatty acid triglycerides, and thus those products are outside the scope of the present claims. "EE" indicates omega-3 fatty acid ethyl esters.

Applicants also sold some of those EPAX products in the U.S. However, the only eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester EPAX products sold in the United States before the July 11, 2002, priority date of the present application were EPAX 5500EE and EPAX 6000EE. The specifications for those products are submitted herewith.

Certain documents state that EPAX's "Marine Omega-3" formula can, among other things, lower serum triglycerides. *See, e.g.,* "Your Heart's Desire," EPAX marketing information, p. 5, submitted herewith. And another document states that "Pronova's unique purification process virtually eliminates regurgitation and also PCBs, heavy metals, and other man-made pollutants."[2] *See, e.g.,* EPAX marketing information distributed after July 11, 2002. Man-made pollutants include brominated flame retardants, PCBs, PCDDs, PCDFs, and TE-PCBs.

However, unlike Omacor®, the EPAX products containing eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester do not fall within the scope of the present claims at least because those products are health supplements, not pharmaceutical compositions as presently claimed, and they did not comprise a marine

[2] Applicants note that that document refers to a product containing 60% omega-3. As can be seen from EPAX's product list, submitted herewith, only EPAX 1050TG - comprising triglycerides - contains such a concentration of EPA and DHA.

oil which comprises EPA ethyl ester and DHA ethyl ester in a pharmaceutically effective concentration to therapeutically treat hypertriglyceridaemia.

The concentrations of EPA ethyl ester (EPA EE) and DHA ethyl ester (DHA EE) in the two EPAX products sold in the U.S. prior to the priority date of the present application are shown below:[3]

	EPA EE	DHA EE	EPA EE + DHA EE	Total Omega-3 EE
EPAX 5500 EE	30% (280 mg/g)	20% (180 mg/g)	55% --	-- --
EPAX 6000 EE	33% (300 mg/g)	22% (200 mg/g)	60% --	-- (600 mg/g)

EPAX's website indicates that "[t]he indication/condition-specific EPAX formulas are designed with various EPA/DHA ratios and concentrations depending on area of use it addresses. The formulas are [the] result of years of clinical research, testing and validation." Two EPAX products are recommended for cardiovascular health: EPAX 6000 EE and EPAX 5500 EE. As shown in the table above, EPAX 6000 EE comprises 60% EPA EE + DHA EE and EPAX 5500 EE comprises 55% EPA EE + DHA EE. Accordingly, those EPAX products differ from Omacor® at least in terms of their concentration of EPA ethyl ester and DHA ethyl ester. It is the concentration of those esters that provides the increased therapeutic benefits of Omacor®.

Applicants have performed a clinical study comparing the uptake and effect on lipid profile[4] of three compositions, albeit on subjects with "relatively low triglyceride

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[3] Information taken from EPAX specifications, copies of which are submitted herewith.

levels." The results were published in Bryhn et al., "The bioavailability and pharmacodynamics of different concentrations of omega-3 acid ethyl esters," *Prostaglandins, Leukotrienes and Essential Fatty Acids* 75:19-24 (2006) ("Bryhn article"), a copy of which is submitted herewith.

Each of the three compositions tested comprised EPA ethyl ester and DHA ethyl ester in the same ratio (approximately 1.0 : 0.8) but the concentration of those esters in the compositions differed, as shown below:

EPA EE + DHA EE	Total Omega-3 EE
62.5%	71%
80%	88.5%
85%	93.5%

By administering different volumes of each of the three compositions, subjects received the same amount (5.1 g) of EPA ethyl ester and DHA ethyl ester per day.

In the article, the authors state:

> Concentrated omega-3 fatty acid formulations are very effective in lowering TGs. Even in subjects with essentially normal triglyceride values at study entry (approximately 130 mg/dl), the 85% and the 80% EPA/DHA concentrations lowered TGs by about 15%. In contrast, the 62.5% concentration had little effect on TGs. Even though the subjects in the 62.5% treatment group had somewhat higher baseline triglyceride levels (approximately 150 mg/dl), this concentration, with the same omega-3 fatty acid content as the 85% and 80% concentrations, did not produce a meaningful impact on the triglyceride level.

Bryhn article at page 22. While the authors offered various hypotheses as to the reason for the differences, "[t]he key finding of this study is that formulations with [the] same

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[4] The effect parameters in this study were the blood lipid fractions for TGs and cholesterol.

amount of omega-3 fatty acids, but with different concentrations of active ingredients, yield differences in uptake and effect properties." *Id.* at 23.

Based on those results, it can be concluded that EPAX products containing eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester, which are health supplements, not pharmaceutical compositions, do not comprise EPA ethyl ester and DHA ethyl ester in a pharmaceutically effective concentration to therapeutically treat hypertriglyceridaemia. Accordingly, those products do not fall within the scope of the present claims at least because those products are health supplements, not pharmaceutical compositions as presently claimed, and they do not comprise a marine oil which comprises EPA ethyl ester and DHA ethyl ester in a concentration that is pharmaceutically effective to therapeutically treat hypertriglyceridaemia.

Accordingly, Applicants respectfully request the entry of the amendments contained herein and the timely allowance of new claims 32-58.

If the Examiner has any questions regarding this amendment or the accompanying Information Disclosure Statement, she is invited to call the undersigned at 202-408-4173.

If there is any fee due in connection with the filing of this Supplemental Preliminary Amendment or the accompanying Information Disclosure Statement, please charge the fee to Deposit Account 06-0916.

Respectfully submitted,

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By: Reg. No. 41,469

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